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10/535,042	01/09/2006	Michael R. Downes	SALK3140-01	2218

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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,042	DOWNES ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,10-15,18-22 and 31-33* is/are pending in the application.

4a) Of the above claim(s) *1-3,6-8,10-13,21,22 and 31-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Definition of representation*.

DETAILED ACTION

Application Status

1. By virtue of a preliminary amendment filed on 04/30/2008, claims 4-5, 9, 16-17, 23-30 and 34-37 have been canceled; and claims 14, 19 and 31 have been amended.

Claims 1-3, 6-8, 10-15, 18-22 and 31-33 are pending in this instant case.

Election

2. Applicant's election with traverse of Group III, (Claims 14-15 and 18-20) in the reply filed on 08/03/2007 is acknowledged. The traversal is on the ground(s) that all the claims "are related to one another" (see bottom of page 7 Remarks filed on 4/30/2008) and "a thorough search of any one group would, of necessity, require a search of the other, related group(s)" (see top of page 7 Remarks filed on 4/30/2008). This is not found persuasive because the claims in Group I are limited to structural definitions alone, thus, to share unity of invention, the Groups must share the structure of the composition of FXR crystal, which is not the case. Applicants also argue that once the one group is searched, all the individual pieces on all other groups would have been searched; thus, no search burden can be cited to restrict the independent inventions. The Examiner disagrees because a through search of said crystal does not automatically results in through search result of other groups, which are drawn to methods and small molecules which binds to the FXR in non-crystalline form, wherein each limitations are distinct from each other. The requirement is still deemed proper and is therefore made FINAL. Claims 1-22 are pending in the instant application.

Claims 1-3, 6-8, 10-13, 21-22 and 31-33 are withdrawn.

Claims 14-15 and 18-20 will be examined herein.

Priority

3. The instant application is a 371 filing of the International Application No. PCT/US03/36548 filed on 11/14/2003, which claims benefit of 60/426,665 filed on 11/15/2002 and claims benefit of 60/426,668 filed on 11/15/2002, as requested in the declaration. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

Applicant's claim no foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

4. The information disclosure statement (IDS) filed on 3/30/2006 has been reviewed, and its references have been considered as shown in the attached copy.

Claim Objections

5. Claims 14, 15 and 18-20 are objected to because of the following informalities:

(a) Claims 14 and 19 recites "crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex". As written, Claims recites

"molecular complex" twice. It should be --- "crystals of said FXR molecule or molecular complex, or a homologue of said FXR molecule or molecular complex"---, with a comma in between, seperating the "FXR" and "homologue of said FXR" for better clarification of the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 14, 15 and 18-20 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14 (Claims 15 and 18 dependent therefrom) are drawn to a method of predicting a molecule capable of binding to a farnesoid X receptor (FXR) molecule, said method comprising: modeling a test molecule that potentially interacts with the composition comprising the ligand binding domain of a farnesoid X receptor(FXR) in crystalline form, wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof, wherein said structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR

molecule or molecular complex. Claim 19 (Claim 20 dependent therefrom) is drawn to a method of identifying a compound with agonist, partial agonist, or antagonist activity with respect to a farnesoid X receptor (FXR) molecule, said method comprising: (a) modeling a test compound that potentially interacts with file ligand binding domain of said FXR molecule or a fragment thereof, wherein said ligand binding domain is defined by a plurality, of structure coordinates of a crystalline form of the ligand binding domain of a FXR molecule or a fragment thereof, wherein said plurality, of structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex; and (b) determining file ability of said test compound to modulate the activity of said FXR molecule in the optional presence of a known FXR agonist.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. While MPEP § 2163

acknowledges that in certain situations "one species adequately supports a genus," it is also acknowledges that "for inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The specification discloses only a single species of claimed genus method for predicting a test compound capable of binding to human FXR (farnesoid X receptor) molecule ligand binding domain (i.e., residues 248-476 of SEQ ID NO: 1); or identifying a test compound with agonist, partial agonist, or antagonist activity to said human FXR molecule ligand binding domain (i.e., residues 248-476 of SEQ ID NO: 1); said method comprise modeling a test compound that potentially interact with said FXR ligand binding domain by the structure coordinates of Appendix 1 (see instant specification, page 64). However, the breadth of claims 14, 18 and 19 encompasses step of modeling a test compound with a structure coordinate of any farnesoid X receptor ligand binding domain (or any homologue of said any FXR ligand binding domain) or a fragment thereof, or a portion of coordinates in Appendix 1; wherein said any FXR ligand binding domain is defined by any two or more coordinates of any FXR with any ligand binding domain (or any homologue of said any FXR); or any fragment thereof. Claims 14 and 19 are not limited to modeling by a computer algorithm and encompass

any way of modeling (drawing structure of a test compound, for example). The recited term (i.e., "plurality of structure coordinates" "set forth in Appendix 1") in Claims 15 and 20 also encompasses any portion (as small as an atom, for example) of coordinates in Appendix 1; thus, method of claims 15 and 20 encompasses step of modeling any two coordinates from Appendix 1. Claims 14 and 19 (Claims 15, 18 and 20 dependent therefrom) recite "said structure coordinates are derived from X-ray diffraction" (emphasis added); and the recited term "derived" in Claims do not limit a structure coordinate to the structure coordinates which must comes from the X-ray diffraction of a FXR (or homologue thereof) crystal. Furthermore, Claim 19 recites the term "modulate the activity of said FXR molecule" and one skilled in the art would not know what kind of activity is encompassed by the instant claim; and can not possess the full scope of claimed invention to identify any compound with agonist, partial agonist, or antagonist of FXR molecule. The instant specification fails to disclose a method comprising modeling by one species of Appendix 1, whereas the instant claims encompass the claimed genus method which encompasses widely variant species as described in the breadth of claims above, including a method of modeling a test compound with "plurality of structure coordinates" (as recited in Claims 14 and 19; e.g., as small as two coordinates) of any FXR domain, any FXR homolog ligand binding domain (or any fragment thereof) for modeling a test compound. The prior art does not describe any structure coordinates for any FXR ligand binding domain (or any FXR homologue thereof), or any fragment thereof that is commensurate with the claimed scope. Because the instant method step encompass very widely varying genus step of using

any FXR ligand binding domain coordinates or any FXR homolog coordinate thereof; the instant specification and prior art can not describe the sufficient correlation between the structure of any FXR ligand binding domain coordinates (or homolog FXR thereof) to a function of modeling a test compound. As described above, the method of genus encompassing unlimited structural variation by the claim(s) is not described sufficiently to correlate to the function of the instant invention by the specification and prior arts. Thus, given the lack of structure and functional correlation of claimed genus method, and lack of description of a representative number of structural coordinates (i.e., structural coordinate of any FXR ligand binding domain, or FXR ligand binding domain homolog thereof, for modeling a test compound; the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

7. Claims 14, 15 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, first paragraph, scope of enablement, because the specification, while being enabling for a method of predicting a molecule capable of binding to a human FXR ligand binding domain (i.e., residues 248-476 of SEQ ID NO: 1); or identifying a compound with agonist, partial agonist, or antagonist activity to a human FXR ligand binding domain (i.e., residues 248-476 of SEQ ID NO: 1) by method step comprising: modeling a test compound with the structure coordinates of Appendix 1 *in silico*; does not reasonably provide enablement for a method encompassing any step of modeling a test compound with any structure coordinate of any farnesoid X receptor ligand binding domain (or any

homologue of said any FXR ligand binding domain), or a fragment thereof, or any portion of coordinates in Appendix 1; wherein said any FXR ligand binding domain is defind by any two or more coordinates of any FXR with any ligand binding domain (or any homologue of said any FXR); or any fragment thereof.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "the language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art

is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims are so broad as to encompass a method step of modeling a test compound with a structure coordinate of any farnesoid X receptor ligand binding domain (or any homologue of said any FXR ligand binding domain) or a fragment thereof, or a portion of coordinates in Appendix 1; wherein said any FXR ligand binding domain is defind by any two or more coordinates of any FXR with any ligand binding domain (or any homologue of said any FXR); or any fragment thereof. Claims 14 and 19 are not limited to modeling by a computer algorithm and encompass any way of modeling (drawing structure of a test compound, for example). The recited term (i.e., "plurality of structure coordinates" "set forth in Appendix 1") in Claims 15 and 20 also encompasses any portion (as small as an atom, for example) of coordinates in Appendix 1; thus, method of claims 15 and 20 encompasses step of modeling any two coordinates from Appendix 1. Claims 14 and 19 (Claims 15, 18 and 20 dependent therefrom) recite "said structure coordinates are derived from X-ray diffraction" (emphasis added); and the recited term "derived" in Claims do not limit a structure coordinate to the structure coordinates which must comes from the X-ray diffraction of a FXR (or homologue thereof) crystal. Furthermore, Claim 19 recites the term "modulate the activity of said FXR molecule" and one skilled in the art would not know what kind of activity is encompassed by the instant claim; and can not possess the full scope of claimed invention to identify any compound with agonist, partial agonist, or antagonist of FXR molecule. The scope of the claims is not commensurate

with the enablement provided by the specification, particularly with respect to the recited method step of modeling a test compound with any FXR ligand binding domain, which is defined by any plurality of structure coordinates (including as small as two coordinates) from the Appendix 1, for example. In this case, the specification is enabling only for a method for modeling a test compound by the coordinates of Appendix 1 *in silico*.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: At the time of the invention, methods of modeling a test compound with a potential interaction between the compound and a protein using a 3-D structure of a protein to a known structural coordinate and computing a computer model of a ligand to ligand binding pocket using a known binding pocket structure. However, while methods of predicting or identifying a test compound association with a protein using a known three dimensional structure of protein and binding pocket of a protein using a set of structure coordinates was known, Lambert et al. (US Patent Application Publication 2004/0137518) acknowledges that "potential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, §0017). Flower D.R. (2002, Drug Design Cutting Edge Approaches, The Royal Society of Chemistry, p. 21-27) also acknowledge that "a well-established technique and automated methods. Problem still exist, however, the fitting together of protein domains in a multi-domain protein, the determination of the most likely conformation of protein loops, the correct positioning of amino acid side chains, flexible ligand docking – to name only a few" (emphasis added, see p 25, lines 18-21). Further, it was well-known in the prior art that polypeptides having disparate functions can share similar 3-D

structures. For example, Hegyi et al. [*J Mol Biol* (1999) 288:147-164] teaches that an isomerase, an oxidoreductase, a hydrolase, and a lyase all share the same TIM-barrel fold (p. 148, left column, and Figure 1). Thus, the full scope of encompassed method of using any structure coordinates of any homologue of FXR molecules (including any variant (or derived) structure coordinates of Appendix 1) cannot predict and/or identify a compound that binds, or with agonist or antagonist activity because of high unpredictability of test compound based on model structure, wherein the model structure encompasses very widely varying structure coordinates. Thus, a skilled artisan would have recognized that there was a high level of unpredictability in method of modeling a test compound with any FXR ligand binding domain structure coordinates; or any model structure coordinates of any FXR homologue from any portion of known 3-D structure coordinates Appendix 1, for the relevant use of instant method for predicting and/or identifying a agonist or antagonist compound, wherein the step involves just modeling of a test compound (in silico or not) with any ligand binding domain of any FXR, or any homolog thereof, or any portion thereof; or any plurality of coordinates in Appendix 1, or a portion thereof.

The amount of direction provided by the inventor and The existence of working examples: The specification suggest a method for evaluating a potential association of an entity with a protein or active site using a model with a certain RMSD compared 3-D structure of the human IRRK having structural coordinates of Figure 3. The prior art by Hubbard et al. (1997, The EMBO Journal, Vol. 16, p. 5573-5581) teach a method of using the 3-D structure of human IRRK, which is within the scope of the instant claims.

The specification fails to disclose a method for evaluating a potential of an entity to associate with a protein using a 3-D structure of any other protein or variant structures thereof that is encompassed by the claims. Further, the specification fails to provide guidance for method for displaying 3-D structures of any other protein that is encompassed by the scope of the claims.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of modeling a test compound with a FXR protein by creating a three dimensional structure in a computer by the coordinates Appendix 1 was established, it was not routine in the art to create a unlimited number of 3-D structures (including a coordinates of any FXR homologues, or fragment thereof) as encompassed by the claims without guidance as to which of those structure coordinates are useful in accordance with the asserted utility of the claimed invention, *i.e.,* to provide useful structural information that assists the predictability and/or identification of a test compound with agonist or antagonist activity to FXR molecules *in vivo*.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable

correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the genus method for predicting a molecule capable of binding to FXR molecule, or for identifying a compound with agonist, partial agonist, or antagonist activity to FXR molecule, according to the full scope of claimed method which comprises modeling a test compound, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 14, 15 and 18-20 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claim is drawn to a method of computerized, *i.e., in silico,* screening of FXR binding and modulating agents. The claim is viewed as an "abstract idea", *i.e.,* a "judicial exception", since the method involves manipulation of data using a computer algorithm. According to MPEP 2106.IV, "A claimed invention is directed to a practical application of a 35 U.S.C. 101 judicial exception when it: (A) "transforms" an article or physical object to a different state or thing; or (B) otherwise produces a useful, concrete and tangible result". The method of claims 14, 15 and 18-20 do not "transform" the data to a "different state or thing" and thus, to qualify as patent eligible subject matter, the

claimed invention, as a whole, must accomplish a practical application. That is, it must produce a "useful, concrete and tangible result." *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 1373, 47 USPQ2d 1596, 1601-02 (Fed. Cir. 1998). Note that the "useful result" aspect of the practical application test requires significant functionality to be present. See *Arrhythmia Research Tech. v. Corazonix Corp.*, 958 F.2d 1053, 1057, 22 USPQ2d 1033, 1036 (Fed. Cir. 1992). In this case, the method of claims 14, 15 and 18-20 does not produce a "useful, concrete and tangible result." While applicant may argue the method of claims 14, 15 and 18-20, being a method of predicting a molecule or identifying a compound, would provide a result set of a number of lead compounds with an increased probability of binding to the protein whose structure was input. However, it is noted that there is no active method step that *selects* for compounds that bind and/or modulate the protein represented by the 3-D model or structural coordinates that would provide a result set of a number of lead compounds with an increased probability of binding to the FXR protein whose structure was input. As such, the claimed method is not deemed to have a "practical application" and thus the claimed invention is considered to be non-statutory subject matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 14, 15 and 18-20 are rejected under 35 U.S.C. 102(b) as being anticipated by McKinney (Environmental Health Perspectives, 1989, Volume 82, pages 323-336).

Claim 14 (Claims 15 and 18 dependent therefrom) is drawn to a method of predicting a molecule capable of binding to a farnesoid X receptor (FXR) molecule, said method comprising: modeling a test molecule that potentially interacts with the composition comprising the ligand binding domain of a farnesoid X receptor(FXR) in crystalline form, wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof, wherein said structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex. Claim 19 (Claim 20 dependent therefrom) 19. (Currently amended) is drawn to a method of identifying a compound with agonist, partial agonist, or antagonist activity with respect to a farnesoid X receptor (FXR) molecule, said method comprising: (a) modeling a test compound that potentially interacts with file ligand binding domain of said FXR molecule or a fragment thereof, wherein said ligand binding domain is defined by a plurality, of structure coordinates of a crystalline form of the ligand binding domain of a FXR molecule or a fragment thereof, wherein said plurality, of structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex; and (b) determining file ability of said test

compound to modulate the activity of said FXR molecule in the optional presence of a known FXR agonist.

Claims 14, 15 and 18 have only one active step, i.e., modeling a test molecule that potentially interacts with a composition comprising the ligand binding domain of a farnesoid X receptor. The recitation of "wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof, wherein said structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex" is merely describing the ligand binding domain of previously recited FXR and is not a limitation for an active step in claimed method in Claim 14 (Claims 15 and 18 dependent therefrom). Also, the recitation of Claims 15 merely further describe the "said plurality of structure coordinates" which describe the ligand binding domain in Claim 14; thus, it is not a limitation having an active method step.

Claims 19 and 20 have only two active steps, i.e., modeling a test molecule that potentially interacts with a composition comprising the ligand binding domain of a farnesoid X receptor; and determining the ability of said test compound to modulate the activity of said FXR molecule. The recitation of "wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof, wherein said plurality of structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex" is

merely describing the ligand binding domain of previously recited FXR and is not a limitation for an active method step in Claims 19 and 20. Also, the recitation of Claims 15 merely further describe the "said plurality of structure coordinates" which describe the ligand binding domain in Claim 14; thus, it is not a limitation having an active method step.

McKinney teaches a method of modeling a ligand shown in Figure 3 which is generated by a computer graphic, which meets the claimed method step (i.e., modeling a test compound) in Claims 14, 15, 18, 19 (in part) and 20 (in part). The recited term "representation of a FXR molecule" in Claim 18 (emphasis added) does not limit to the any specific FXR molecule because of the term "representation" which encompasses any "image or likeness of something" (see definition of representation in the attachment); thus, any topographical or surface structure shown in Figure 3 of McKinney represent FXR molecule or fragment thereof. The topographical region or any surface shape generated by molecule other than the ligand itself in the Figure 3 of McKinney is a representation of a molecule that is in any FXR protein. Thus, the interaction between the ligand and the region or surface shown by McKinney meets the limitation of test molecule being developed using a computer algorithm to predict a three-dimensional representation of a test molecule interacting with FXR molecule based upon a three-dimensional representation of FXR molecule or fragment thereof, as recited in Claim 18. The fact that McKinney teach the step of a ligand interacting with a surface by inserting into a crevice or interacting with any surface having concave shaped site meets the limitation of determining the ability of said test compound to

modulate the activity of said FXR molecule since how much or what kind of activity being modulated is not limited to any activity of FXR molecule fragment thereof, wherein said FXR molecule is any FXR molecule having any crevice and/or concaved site in any surface of any place of said any FXR molecule. Thus, the method of McKinney meets all limitation of Claims 14-15, 18 and 19-20.

Comment [AK1]: I think my 102 is solid so I deleted 103. Thank you.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652